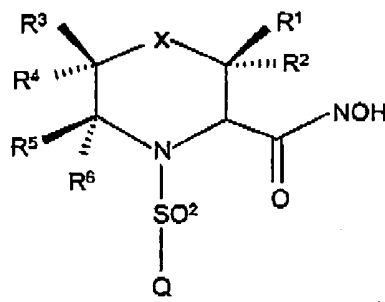


IN THE CLAIMS:

Claims 1 - 60 (Cancelled)

Claim 61 (Currently Amended) A method of inhibiting the cleavage of TNF- α from cell membranes in a human comprising administering to such human an effective amount of a hydroxamic acid compound comprising ~~a suitable substituted~~ the formula:



or the pharmaceutically acceptable salt thereof, wherein

X is oxygen, sulfur, SO, SO₂ or NR⁷;

R¹, R², R³, R⁴, R⁵ and R⁶ are selected from the group consisting of
hydrogen, hydroxy, NH₂, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl(C₂-C₆)alkenyl,
(C₂-C₉)heteroaryl(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl(C₂-C₆)alkynyl, (C₂-
C₉)heteroaryl(C₂-C₆)alkynyl, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, (C₁-C₆)alkylthio,
(C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₂-
C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-
C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₃-C₆)cycloalkyl, (C₁-
C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-
C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-
(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-;

wherein said (C₁-C₆)alkyl is optionally substituted by one or two groups selected from (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, trifluoromethyl, halo, -CN, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino or ((C₁-C₆)alkyl)₂amino;

R⁷ is hydrogen; (C₁-C₆)alkyl optionally substituted by one or more of hydroxy, -CN, (C₁-C₆)alkylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroarylamino, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-; (C₆-C₁₀)arylsulfonyl; (C₁-C₆)alkylsulfonyl; (C₁-C₆)alkyl-NH-(C=O)-; (C₁-C₆)alkoxy-(C=O)-; (C₁-C₆)alkyl-(C=O)-; [(C₁-C₆)alkyl]₂-N-(C=O)-; or (R⁸R⁹N)-(C=O) where R⁸ and R⁹ are taken together with the nitrogen that they are attached to form a ring selected from azetidiny, pyrrolidinyl, piperidinyl, morpholinyl and thiomorphonyl; where Q is (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₁₀)heteroaryl, (C₁-C₁₀)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₁-C₁₀)heteroaryl(C₁-C₆)alkoxy(C₁-C₁₀)heteroaryl;

with the proviso that when X is SO or SO₂ and R₃ and R₄ are a substituent comprising a heteroatom, the heteroatom cannot be bonded to the ring;

and with the proviso that at least one of R¹-R⁶ must be (C₁-C₆)alkyl;

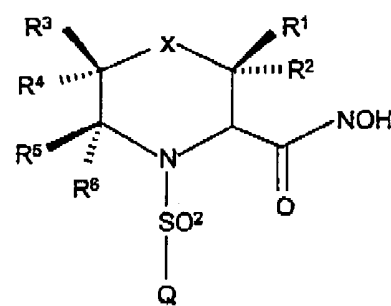
and with the proviso that when X is oxygen or sulfur and R³-R⁶ are each hydrogen then R¹ and R² cannot both be methyl;

that possesses an in vitro IC₅₀ selectivity for TACE over MMP-1 of at least 100 fold; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claims 62 - 80 (Cancelled)

Claim 81 (Currently Amended) ~~A method of inhibiting the cleavage of TNF- α from cell membranes in a human comprising administering to such human an effective amount of a disubstituted hydroxamic acid compound comprising a suitably substituted (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₁₀)heteroaryl, (C₁-C₁₀)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₁-C₁₀)heteroaryl(C₁-C₆)alkoxy(C₁-C₁₀)heteroaryl;~~ that The method of claim 61 wherein said hydroxamic acid compound possesses an in vitro IC₅₀ selectivity for TACE over MMP-1 of at least 500 fold; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claim 82 (Currently Amended) A method of inhibiting the cleavage of TNF- α from cell membranes without inhibiting MMP-1 in a mammal comprising: administering to said mammal an effective amount of a hydroxamic acid compound that possesses at least 100 fold IC₅₀ selectivity for TACE over MMP-1, said hydroxamic acid compound comprising a the formula:



or the pharmaceutically acceptable salt thereof, wherein

X is oxygen, sulfur, SO, SO₂ or NR⁷;

R¹, R², R³, R⁴, R⁵ and R⁶ are selected from the group consisting of

hydrogen, hydroxy, NH₂, -CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl, (C₂-C₆)alkenyl, (C₂-C₉)heteroaryl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl, (C₂-C₆)alkynyl, (C₂-C₉)heteroaryl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkoxy, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroaryl, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-;

wherein said (C₁-C₆)alkyl is optionally substituted by one or two groups

selected from (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, trifluoromethyl, halo, -CN, (C₆-C₁₀)aryl, (C₂-C₉)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroaryl, (C₂-C₉)heteroarylthio, (C₂-C₉)heteroaryloxy, (C₆-C₁₀)aryl, (C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl, (C₁-C₆)alkoxy, (C₂-C₉)heteroaryl, (C₁-C₆)alkoxy, (C₁-C₆)acylamino, (C₁-C₆)acylthio, (C₁-C₆)acyloxy, (C₁-

(C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₆)alkylamino or ((C₁-C₆)alkyl)₂amino;

R⁷ is hydrogen; (C₁-C₆)alkyl optionally substituted by one or more of hydroxy, -CN, (C₁-C₆)alkylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkoxy, perfluoro(C₁-C₆)alkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryltio, (C₆-C₁₀)aryloxy, (C₂-C₉)heteroaryl, (C₂-C₉)heteroarylamino, (C₂-C₉)heteroarylcycloalkyl, (C₁-C₆)alkyl(hydroxymethylene), piperidyl, (C₁-C₆)alkylpiperidyl, (C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy-(C=O)-, -CO₂H, (C₁-C₆)alkyl-NH-(C=O)-, and [(C₁-C₆)alkyl]₂-N-(C=O)-; (C₆-C₁₀)arylsulfonyl; (C₁-C₆)alkylsulfonyl; (C₁-C₆)alkyl-NH-(C=O)-; (C₁-C₆)alkoxy-(C=O)-; (C₁-C₆)alkyl-(C=O)-; [(C₁-C₆)alkyl]₂-N-(C=O)-; or (R⁸R⁹N)-(C=O) where R⁸ and R⁹ are taken together with the nitrogen that they are attached to form a ring selected from azetidyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorphonyl; where Q is (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl, (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₆-C₁₀)aryl, or (C₂-C₉)heteroaryl(C₁-C₆)alkoxy(C₂-C₉)heteroaryl wherein each of said (C₆-C₁₀)aryl or (C₂-C₉)heteroaryl groups may optionally be substituted by one of more substituents independently selected from halo, -CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl(C=O)-O-(C₁-C₆)alkyl, H(O=C), H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-

C_6 alkyl] $_2$ N-(C=O)-, H_2N (C=O)- (C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)- (C₁-C₆)alkyl,
 [(C₁-C₆)alkyl] $_2$ N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH, (C₁-
 C_6 alkyl(C=O)-[NH] (C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl] (C₁-C₆)alkyl, (C₁-
 C_6 alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, (C₁-
 C_6 alkyl-SO₂-[N-(C₁-C₆)alkyl]-, H_2N -SO₂-, H_2N -SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-
 (C₁-C₆)alkyl, [(C₁-C₆)alkyl] $_2$ N-SO₂-(C₁-C₆)alkyl, CF₃SO₃-, (C₁-C₆)alkyl-SO₃-, phenyl,
 phenyl(C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl;

with the proviso that when X is SO or SO₂ and R₃ and R₄ are a substituent comprising a heteroatom, the heteroatom cannot be bonded to the ring;

and with the proviso that at least one of R¹-R⁶ must be (C₁-C₆)alkyl;

and with the proviso that when X is oxygen or sulfur and R³-R⁶ are each hydrogen then R¹ and R² cannot both be methyl; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Claim 83 (Original) The method of Claim 82 wherein said hydroxamic acid compound possesses at least 500 fold IC₅₀ selectivity for TACE over MMP-1.